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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	15

DATE MAILED: 06/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,111	INPANBUTR, NONGNUCH	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 18-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 18-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on March 31, 2003 and January 2, 2003 has been entered.

The addition of claims 26-40 in Applicant's amendments filed January 2, 2003 is acknowledged.

The claims are now drawn to the treatment of SCC 2/88 squamous cell lines and therefore, the outstanding rejections under 112, first paragraph is withdrawn.

Warning

Applicant is advised that should claim 26 be found allowable, claims 34 and 40 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). these claims are essentially the same because they are drawn to a method of administering a pharmacologically active (therapeutic) agents to a dog.

Moreover, by the similar reason, should claim 27 be found allowable, claim 38 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. They

are drawn to the method of administering to a dog the same compounds. Additionally, should claim 29 be found allowable, claim 39 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. They are drawn to the method of administering to a dog the same amounts of vitamin D compounds.

New Ground of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-12, 18-26, 28-37, and 39-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vitamin D3, analog V, and EB 1089, does not reasonably provide enablement for other vitamin D analog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The claims are very broad. They encompassed all vitamin D analogs. The specification fails to provide any guidance as to how to select a suitable vitamin D compounds for practicing the instant invention. Moreover, the specification fails to provide working examples of vitamin D compounds, other than those disclosed in page 1, lines 22-24, for treating squamous carcinoma cell lines. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. For example, in Bouillon et al. Endocrine Reviews, 995; 16(2):200-257, it teaches that the presence of 1α-hydroxyl group is essential to cell differentiation and those analogs lacking the 1α-hydroxyl group will not effectively bind to the nVDR and initiate cell differentiation (See Bouillon et al., page 218, col. 2, last paragraph). It is apparent that different vitamin D analogs have vastly different biological effects (See Table 2, from page 208-214). Without defining the class of vitamin D compounds suitable for the instant invention, one of skilled in the art would be required to perform undue experimentation to ascertain the vitamin D compounds useful in the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 18-26, 28-37, and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "vitamin D analog" recited in the claims 1, 6-12, 18-26, 28-37, and 39-40 renders the claims indefinite because it is unclear what vitamin D compounds are encompassed by the claims. The instant specification attempts to define what vitamin D analogs are encompassed by the claims; however, the disclosure in page 1, lines 22-24 in the instant specification merely lists three examples of what vitamin D compounds can be used in the instant invention. As discussed above, a minor changes of vitamin D structure could result in significant change pharmacologically. Therefore, it is not clear to one of ordinary skill in the art what vitamin D compounds, other than the ones disclosed in page 1, lines 22-24, would be encompassed by the claims herein.

The expression "treating ... a canine squamous carcinoma cell line,... comprising the step of feeding a dog a therapeutic agent" recited in claim 1 renders the claims indefinite as to the recited method. It is unclear if the method is drawn to an *in vitro* or *in vivo* method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5, 7-12 and 23-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boggolini et al. (USPN 5,087,619) and Abdaimi et al. (Cancer Research, 1999; 59:3325-3328), insofar as it relates to the *in vivo* method of treating squamous carcinoma.

Boggiolini et al. teaches a method of treating neoplastic diseases in a warm-blooded animal comprising administering an effective amount of a vitamin D3 analogue (e.g., 1,25 (OH)2 D3 and 1,2-16 delta-23-yne-D3) (see for example tables III and IV, claim 20 and abstract). Boggiolini et al. also teaches the vitamin D compounds therein are useful in effectively against human squamous carcinoma cell lines (See col. 15, line 32-48, Table III). Boggiolini et al. also teaches vitamin D3 analogues in oral dosage forms such as capsules, see col. 21, lines 37-40. Pharmaceutically acceptable carrier materials may be incorporated in capsules, such as starch, magnesium stearate,

lactose, peppermint oil (flavoring agent) (see in particular col. 21, line 37 to col. 22, line 27). Boggiolini et al. also teaches that the dosage for the vitamin D3 analogues is 0.1 to 10 microgram per day (see col. 11, lines 16-24).

Abdaimi et al. teaches that EB1089 is known to inhibit cell proliferation and is useful against squamous carcinoma (See page 3327, col. 2, third paragraph).

Boggolini et al. and Abdaimi et al. taken together do not teach the doses claimed herein in terms of nmol/Kg, neither do they teach all the pharmaceutical excipients and auxillaries claimed herein. Boggolini et al. and Abdaimi et al. also do not teach the method of treating SCC 2/88 cell lines.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ/express the amounts of active in terms of nmol/Kg. It would have also been obvious to employ any known pharmaceutical excipients and auxillaries in the composition employed in the instant method. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein recited vitamin D compounds to treat squamous cell carcinoma.

One of ordinary skill in the art would have been motivated to employ/express the amounts of active in terms of nmol/Kg because optimization of amounts is within the skill of the artisan and is therefore obvious. Similarly the employment of any known pharmaceutical excipient and/or auxillaries with a known active is within the skill of the artisan and therefore obvious.

One of ordinary skill in the art would have been motivated to employ the herein recited vitamin D compounds to treat squamous cell carcinoma. The preferred vitamin D

compounds herein are known to be useful in treating human squamous carcinoma. Employing the same compounds for treating a canine squamous carcinoma would be reasonably expected to be successful since the compounds herein are known to be useful in any warm-blooded animal for fighting against squamous carcinoma, absent evidence to the contrary (See Boggolini et al.).

Claims 6 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boggolini et al. and Abdaimi et al. as applied to claims 1-5 and 7-12 and in further view of Katzung (Basic and Clinical Pharmacology, p.661-663, 838, 841, 830-832 and 537-538) and Hardman et al. (Goodman and Gilman's The Pharmacological Basis of Therapeutics, p.539), all of record in the previous office action.

Boggiolini et al. and Abdaimi et al. suggest the method of treating canine squamous carcinoma by employing the herein claimed vitamin D compounds.

Boggiolini et al. and Abdaimi et al. taken together do not teach the inclusion of a second active (i.e., bone agent, cytotoxic agent or anti inflammatory agent) in a composition employed in a method of treating cancer.

Katzung teaches that hypercalcemia is a consequence of hypervitaminosis D. Katzung further teaches that bisphosphonates, calcitonin are employed in treating hypercalcemia, see pages 661-663. Katzung also teaches the employment of estrogen inhibitors, mitomycin, vincristine, doxorubicin, fluorouracil for treating different cancers, see page 838 and 841. Katzung further teaches cisplatin, melphalan, and methoxorate

as anti-cancer agents, see pages 830-832. Both Salicylates and Naproxen are known NSAIDS (known for their anti-inflammatory and analgesic properties), 537-538.

Hardman et al. teaches that pain is commonly associated with cancer, see page 539.

It would have been obvious to one of ordinary skill at the time the invention at the time the invention was made to employ a second active (i.e., bone agent, cytotoxic agent or anti inflammatory agent) in a composition employed in a method of treating cancer.

One of ordinary skill in the art would have been motivated to employ bisphosphonates and calcitonin in a method of treating cancer employing a vitamin D3 analogue/derivative because they are known to be employed in methods of preventing and/or treating hypercalcemia associated with vitamin D administration. One of ordinary skill in the art would have been motivated to employ Salicylates and Naproxen, known NSAIDS, known for their anti-inflammatory and analgesic properties, in a method of treating cancer because pain is known to be associated with cancer.

One of ordinary skill in the art would have been motivated to employ estrogen inhibitors, mitomycin, vincristine, doxorubicin, fluorouracil cisplatin, melphalan, and methoxorate along with Vitamin D derivatives in a method of treating cancer. Estrogen inhibitors, mitomycin, vincristine, doxorubicin, fluorouracil cisplatin, melphalan, and methoxorate are known to be employed in methods of treating cancer. Combining two agents which are known to be useful to treat cancer individually into a single

composition useful for the very same purpose (i.e. treating cancer) is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

Response to Arguments

Applicant's arguments with respect to claims 1-12 and 18-40 have been considered but are moot in view of the new ground(s) of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
Patent Examiner
Art Unit 1617
June 5, 2003